1. Claims 233-237,239-243,246-253,255-261,274-286 are under consideration.

2. The objection to the amendment filed 8/30/07 under 35 U.S.C. 132(a) because it introduces new matter into the disclosure as enunciated in the previous Office Action is withdrawn in view of applicants arguments.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 233-237,239-242 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no support in the specification as originally filed for the recitation of section (b) in claim 233. The specification (page 35) discloses use of a specific unidentified HL60 cDNA library to isolate cDNA encoding the TNFR 75kD. However, the claims encompass use of HL60 cDNA libraries from cells other than those specifically disclosed in the specification (aka the deposited cell line recited the claims wherein said cell is not the specific cell line disclosed in the specification because it is not the specific cell line used by applicant). However, cDNA libraries made from different HL60 cell lines will differ in DNA content due to spontaneous mutation found in HL60 cells (for example, see Monnat, abstract). Thus, the specification discloses a specific library with specific sequences wherein the claims encompass use of HL60 libraries that contain different sequences. In addition, the specification discloses that the search of said cDNA library yielded the CDNA clone of Figure 4. The claims encompass sequences other than that disclosed in Figure 4. Regarding applicants comments, none

of the cited references provide evidence that the cell line recited in the claims and the cell line used in the specification are identical.

There is no support in the specification as originally filed for claims that recite additional subsequences in the sequence of claim 233, as per above, the specification discloses that the search of said HL60 cDNA library yielded the CDNA clone of Figure 4. The claims encompass sequences other than that disclosed in Figure 4.

The previously enunciated section of this rejection (There is no support in the specification as originally field for recitation in claim 243 of the plasmid PTA 7942 for essentially the same reasons as stated in paragraph 3 of this Office action.) is withdrawn in view of applicants arguments.

Regarding applicants comments, the new matter rejection with regards to Plasmid PTA-7942 has been withdrawn. Regarding applicants comments, there is no support in the specification as originally filed for the recitation of section (b) in claim 233. The specification (page 35) discloses use of a specific unidentified HL60 cDNA library to isolate cDNA encoding the TNFR 75kD. However, the claims encompass use of HL60 cDNA libraries from cells other than those specifically disclosed in the specification (aka the deposited cell line recited the claims wherein said cell is not the specific cell line disclosed in the specification because it is not the specific cell line used by applicant (aka). However, cDNA libraries made from different HL60 cell lines will differ in DNA content due to spontaneous mutation found in HL60 cells (for example, see Monnat, abstract). Thus, the specification discloses a specific library with specific sequences wherein the claims encompass use of HL60 libraries that contain different sequences.

Regarding applicants comments, the cited passages of the specification do not refer to the HL-60 that was used to identify/isolate the nucleic acids encompassed by those recited in the claims as per the specification, page 35. In addition, the specification discloses that the search of said cDNA library yielded the CDNA clone of Figure 4. The claims encompass sequences other than that disclosed in Figure 4. Regarding applicants comments, none of the cited references provide evidence that the cell line recited in the claims and the cell line used in the specification are identical. There is no support in the specification as originally filed for claims that recite additional

subsequences in the sequence of claim 233, as per above, the specification discloses that the search of said HL60 cDNA library yielded the CDNA clone of Figure 4. The claims encompass sequences other than that disclosed in Figure 4.

Applicant has indicated the claims under consideration would be cancelled should the remaining claims be found allowable (see page 12 of the amendment filed 3/15/11).

5. Claims 233-237,239-242 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection of claims 274-279 under this ground of rejection as per enunciated in the previous Office Action is withdrawn in view of applicants arguments.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the . . . claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed inventions.

The only nucleic acid encoding a sequence comprising soluble portions of insoluble TNF binding proteins of a TNF 75 kD receptor disclosed in the specification are those disclosed in the Figures. The cell line recited in part (b) of claim 233 is not the identical cell line as used by applicants in the specification, and therefore said claim encompasses mutants and alleles of the sequences disclosed in the Figures of the instant application. cDNA libraries made from different HL60 cell lines will differ in DNA content due to spontaneous mutation found in HL60 cells (for example, see Monnat, abstract). Thus, the claims would encompass unknown and undescribed mutants and variants of the specific sequences disclosed in the specification wherein the identity of said mutants and variants is unknown and unpredictable. The term “human TNF receptor” (and nucleic acids encoding said molecule) as per used in the specification

clearly encompasses mutants, variants and alleles of said molecule wherein the identity of such molecules is not disclosed in the specification and is unpredictable (see specification, page 2, lines 25-33, page 5, lines 11-25, page 10,lines 3-10, page 11, lines 13-38).

Thus, the written description provided in the specification is not commensurate with the scope of the claimed inventions. In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1404-7 (Fed. Cir. 1997). In University of California v. Eli Lilly and Co., 39 U.S.P.Q.2d 1225 (Fed. Cir. 1995) the inventors claimed a genus of DNA species encoding insulin in different vertebrates or mammals, but had only described a single species of cDNA which encoded rat insulin. The court held that only the nucleic acids species described in the specification (i.e. nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, id. at 1240. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials. . .conception has not been achieved until reduction to practice has occurred", Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd., 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991). Attention is also directed to the decision of The Regents of the University of California v. Eli Lilly and Company (CAFC, July 1997) wherein is stated: The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the

sequence of nucleotides that make up the cDNA. See Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606.

Regarding applicants comments, the only nucleic acid encoding a sequence comprising soluble portions of insoluble TNF binding proteins of a TNF 75 kD receptor disclosed in the specification are those disclosed in the Figures. The cell line recited in part (b) of claim 233 is not the identical cell line as used by applicants in the specification, and therefore said claim encompasses mutants and alleles of the sequences disclosed in the Figures of the instant application. cDNA libraries made from different HL60 cell lines will differ in DNA content due to spontaneous mutation found in HL60 cells (for example, see Monnat, abstract). Thus, the claims would encompass unknown and undescribed mutants and variants of the specific sequences disclosed in the specification wherein the identity of said mutants and variants is unknown and unpredictable. The term "human TNF receptor" (and nucleic acids encoding said molecule) as per used in the specification clearly encompasses mutants, variants and alleles of said molecule wherein the identity of such molecules is not disclosed in the specification and is unpredictable (see specification, page 2, lines 25-33, page 5, lines 11-25, page 10,lines 3-10, page 11, lines 13-38).

Regarding applicants comments, as per above, *the rejection of claims 274-279 under this ground of rejection as per enunciated in the previous Office Action is withdrawn in view applicants arguments*. The remaining rejected claims recite limitations that were not addressed in the Board decision of application 08/444791.

Applicant has indicated the claims under consideration would be cancelled should the remaining claims be found allowable (see page 12 of the amendment filed 3/15/11).

6. Regarding priority for the claimed inventions and the application of prior art, the claimed nucleic acids encoding fusion proteins are not disclosed in the Swiss priority documents. SEQ ID. NO: 27 is not disclosed in said applications. The vectors recited in the claims are also not disclosed in said applications. Also, the correct sequence for the DNA encoding the TNF 75 kD receptor (as per page 35, last paragraph of the specification) is not disclosed in said applications.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 233-237,239-243,246-253,255-261,274-286 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (US Patent 5,395,760) in view of Capon et al. (US Patent 5428130).

Smith et al. teach DNA encoding an insoluble (eg. membrane bound) 75 kD TNF receptor that has the amino acid sequence of SEQ. ID. NO:27 (see Figure 2). Smith et al. teach the soluble extracellular portion of said molecule (see column 4). Smith et al. teach a nucleic acid encoding an IgG1/soluble portion of a 75kD TNF receptor wherein the fusion protein is bivalent for TNF receptor (see column 10, last paragraph). Smith et al. do not teach a nucleic acid encoding an Ig/soluble portion of a 75kD TNF receptor wherein the IG portion lacks the first domain of the constant region. This rejection addresses the TNF-R nucleic acid sequence of claims 233/243 as encompassing SEQ. ID. NO:27. Capon et al. teach DNA encoding Ig/ligand binding fusion proteins (see column 5). Capon et al. teach that the Ig/ligand binding fusion protein can contain the soluble portion of a cell surface receptor (eg. the receptor minus the transmembrane and cytoplasmic domains, see column 8, first complete paragraph). Capon et al. teach that the DNA encoding the Ig portion of the fusion protein can contain at least the hinge, CH2 and CH3 domains of the constant region of an Ig heavy chain or the Fc portion of the heavy chain (see column 10, second paragraph). Capon et al. teach vectors /host cells containing said DNA and use of said cells to produce fusion protein (see column 26-30). Capon teach the use of IgG-1 constant region in said fusion proteins (see claim 3). Capon et al. teach that the ligand binding portion of the Ig/ligand binding fusion protein can be derived from a wide variety of different known cell surface receptors (see column 7, third paragraph from bottom). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Smith et al. teach the nucleic acid sequence encoding an

insoluble (eg. membrane bound) 75kD TNF receptor and DNA encoding bivalent Ig fusion proteins containing said molecule while Capon et al. teach DNA encoding soluble Ig/ligand binding fusion proteins wherein the DNA encoding the Ig portion of the fusion protein can contain at least the hinge, CH2 and CH3 domains of the constant region of an Ig heavy chain and wherein the ligand binding protein is a soluble portion derived from a cell surface receptor. One of ordinary skill in the art would have been motivated to do the aforementioned because Capon et al. teach that the ligand binding portion of the Ig/ligand binding fusion protein can be derived from a wide variety of different known cell surface receptors (see column 7, third paragraph from bottom) and that said fusion proteins have a variety of a uses (see column 4). The IgG1 constant region fragment encoding nucleic acids of pCD4Hgamma1 appear to be the art known nucleic acids encoding the portion of the human IgG1 constant region as per disclosed in Capon et al. In addition, Smith et al. teach a nucleic acid encoding an IgG1/soluble portion of a 75kD TNF receptor wherein the fusion protein is bivalent for TNF receptor.

Regarding applicants comments about the Board decision in application 08/444790, the rejection under consideration in the instant application is not a rejection addressed in said application (aka the Smith et al. patent was not cited in said application**). However, it is noted that said application does now contain such a rejection (signed by Group Director Elliot).** Regarding applicants comments, Smith et al. teach DNA encoding an insoluble (eg. membrane bound) 75 kD TNF receptor that has the amino acid sequence of SEQ. ID. NO:27 (see Figure 2). Smith et al. teach the soluble extracellular portion of said molecule (see column 4). Smith et al. teach DNA encoding an insoluble (eg. membrane bound) 75 kD TNF receptor that has the amino acid sequence of SEQ. ID. NO:27 (see Figure 2). Smith et al. teach the soluble extracellular portion of said molecule (see column 4). Smith et al. teach a nucleic acid encoding an IgG1/soluble portion of a 75kD TNF receptor wherein the fusion protein is **bivalent** for TNF receptor (see column 10, last paragraph). Smith et al. do not teach a nucleic acid encoding an Ig/soluble portion of a 75kD TNF receptor wherein the IG portion lacks the first domain of the constant region. This rejection addresses the TNF-R nucleic acid sequence of claims 233/243 as encompassing SEQ. ID. NO:27. Capon et al. teach DNA encoding Ig/ligand binding fusion proteins (see column 5). Capon et al.

teach that the Ig/ligand binding fusion protein can contain the soluble portion of a cell surface receptor (eg. the receptor minus the transmembrane and cytoplasmic domains, see column 8, first complete paragraph). Capon et al. teach that the DNA encoding the Ig portion of the fusion protein can contain at least the hinge, CH2 and CH3 domains of the constant region of an Ig heavy chain or the Fc portion of the heavy chain (see column 10, second paragraph). Capon et al. teach vectors /host cells containing said DNA and use of said cells to produce fusion protein (see column 26-30). Capon teach the use of IgG-1 constant region in said fusion proteins (see claim 3). Capon et al. teach that the ligand binding portion of the Ig/ligand binding fusion protein can be derived from a wide variety of different known cell surface receptors (see column 7, third paragraph from bottom). Whilst the Smith et al. reference in itself does not teach the claimed invention, it renders obvious the claimed invention in combination with the references cited above. The Smith et al. teaching regarding antibodies which applicant refers to is irrelevant to the claimed invention because the claimed invention is not drawn to antibodies.

Regarding applicants comments about motivation to create the claimed invention, Smith et al. teach a nucleic acid encoding an IgG1/soluble portion of a 75kD TNF receptor wherein the fusion protein is **bivalent** for TNF receptor (see column 10, last paragraph) whilst Capon et al. teach that the DNA encoding the Ig portion of the fusion protein can contain at least the hinge, CH2 and CH3 domains of the constant region of an Ig heavy chain or the Fc portion of the heavy chain (see column 10, second paragraph). The teaching of Capon et al. on column 10, second paragraph is singular and unambiguous. The MPEP section 2123 states:

PATENTS ARE RELEVANT AS PRIOR ART FOR ALL THEY CONTAIN

"The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting In re Lemelson, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)).

Furthermore, as per above, Smith et al. teach a nucleic acid encoding an IgG1/soluble portion of a 75kD TNF receptor whilst Capon et al. teach:

"Typically, such fusions retain at least functionally active hinge, CH2 and CH3 domains of the constant region of an immunoglobulin heavy chain. Thus, ***Capon et al. clearly disclose that the aforementioned form of fusion protein is commonly/typically made in the art.***

In addition, as per Smith et al., column 10, last paragraph, the disclosed chimeric fusion protein can be **bivalent (aka can contain either two copies of the TNF-R** ("A recombinant chimeric antibody molecule may also be produced having TNF-R sequences substituted with **either** or both of the immunoglobulin molecule heavy and light chains …")). Thus, regarding the Lesslauer declaration, the Smith et al. reference **already disclosed** an Ig fusion protein construct **containing two copies of the TNF-R**. Capon et al. teach their fusion protein was a typical form of such a fusion protein commonly made in the art. Furthermore, in KSR Int'l Co. v. Teleflex Inc., 550 U.S. m, 2007 WL 1237837, at "13 (2007) it was stated that "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill".

Regarding applicants comments, on pages 21-25 of the instant amendment, said arguments do not address the teachings of Capon et al. (see column 10, last paragraph) that: "***Typically***, such fusions retain at least functionally active hinge, CH2 and CH3 domains of the constant region of an immunoglobulin heavy chain.". Said fusion protein is the form of fusion protein recited in the claims under consideration. Capon et al. teach that such fusion proteins would be typically made as per column 10

Regarding applicants comments about other inventions taught by Capon et al., the MPEP section 2123 states:

II. NONPREFERRED AND ALTERNATIVE EMBODIMENTS

CONSTITUTE PRIOR ART

Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) (The invention was directed to an epoxy impregnated fiber-reinforced

printed circuit material. The applied prior art reference taught a printed circuit material similar to that of the claims but impregnated with polyester-imide resin instead of epoxy. The reference, however, disclosed that epoxy was known for this use, but that epoxy impregnated circuit boards have "relatively acceptable dimensional stability" and "some degree of flexibility," but are inferior to circuit boards impregnated with polyester-imide resins. The court upheld the rejection concluding that applicant's argument that the reference teaches away from using epoxy was insufficient to overcome the rejection since "Gurley asserted no discovery beyond what was known in the art." 27 F.3d at 554, 31 USPQ2d at 1132.). Furthermore, "[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed…." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

Regarding applicants comments about unexpected results, the claimed inventions are drawn to nucleic acids, cells containing said nucleic acids and a method of use, not proteins. There is no evidence of record regarding unexpected results and the claimed invention (especially nucleic acids and vectors/host cells containing said nucleic acids). Regarding applicants comments, the MPEP section 716.02(d) states:

716.02(d) [R-2] Unexpected Results Commensurate in Scope With Claimed Invention

Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support.".

The claimed inventions are drawn to nucleic acids, not proteins. Regarding applicants comments about section 2116.01, said section deals with the issue of whether a method that use a conventional process and an nonobvious product could be patented (aka In re Ochiai) wherein said case is irrelevant to the issue under consideration.

However, as per the interview of 8/4/2010, the putative "unexpected results" regarding the protein will be addressed. The MPEP section 716.02(e) states:

716.02(e) [R-2] Comparison With Closest Prior Art

An affidavit or declaration under 37 CFR 1.132 must compare the claimed subject matter with ***the closest prior art to be effective to rebut a prima facie case of obviousness****. In re Burckel, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979). "A comparison of the claimed invention with the disclosure of each cited reference to determine the number of claim limitations in common with each reference, bearing in mind the relative importance of particular limitations, will usually yield the closest single prior art reference." In re Merchant, 575 F.2d 865, 868, 197 USPQ 785, 787 (CCPA 1978) (emphasis in original). Where the comparison is not identical with the reference disclosure, deviations therefrom should be explained, In re Finley, 174 F.2d 130, 81 USPQ 383 (CCPA 1949), and if not explained should be noted and evaluated, and if significant, explanation should be required. In re Armstrong, 280 F.2d 132, 126 USPQ 281 (CCPA 1960) (deviations from example were inconsequential).*

In the instant rejection, the closest prior art is the nucleic acid encoding an IgG/soluble portion of a 75kD TNF receptor wherein the fusion protein is bivalent for TNF receptor as per taught by Smith et al. ***However, none of the cited evidence of unexpected results regarding the claimed invention actually compares the instant invention to the closest prior art.***

The Arora declaration filed 3/15/11 does not compare the claimed invention to the closest prior art as per above in Smith et al. It is noted that the two fusion proteins other than the claimed invention which are disclosed in said declaration are not the fusion protein of the prior art (aka ***they do not both possess the intact hinge region and they contain linkers***). **Furthermore, the extracellular domain of the TNFR recited in the claims is 235 amino acids wherein the TNFR used in the two fusion proteins referred to in the Arora declaration are 163 and 179 amino acids in length. Thus, said constructs do not even contain the extracellular domain of the TNFR recited in the claims and known in the prior art.** Therefore, said constructs are not germane to the claimed invention or the prior art.

In addition, the Arora et al. publication addresses the in vitro data disclosed in the Arora declaration and raises numerous points not addressed in the declaration. For example, Arora et al., page 130, second column states:

"The major clinical differences between the actions of the two classes of agents may be related to effects on granulomatous

diseases and infections. Infliximab is efficacious in the treatment of Crohn's disease [5,28,30] and Wegener's granulomatosis [34], whereas etanercept has not demonstrated clinical benefits in these diseases. TNF is an important mediator for maintaining the granulomatous response to control chronic infections: however, total and persistent blockade of the cells that produce this inflammatory cytokine could be detrimental [23]. The use of infliximab has been associated with higher rates of several granulomatous infections compared with etanercept, including coccidioidomycosis, histoplasmosis, listeriosis, salmonellosis, and tuberculosis [35-38]. In addition, it is possible that the combination of high avidity binding to mTNF within the granulomatous tissue, and the ability to bind FcγR and Clq as large Ab complexes, may account for the higher rates of granulomatous infections in patients treated with the anti-TNF mAbs. It is worth noting that not all anti-TNF mAbs are capable of Fc receptor binding and complement fixation. Certolizumab, a monovalent Fab' fragment of an IgGI mAb covalently linked to polyethylene glycol, lacks these functions because it has no Fc region, yet it still appears to be effective in the treatment of RA and Crohn's disease [39]. ".

Thus, Arora et al. indicates that the antiTNF antibodies referred to in the Arora declaration have **clinical efficacy in diseases that etanercept cannot be used to treat**. Whilst Arora et al. indicate that the two antibodies used in the declaration are associated with a greater rate of certain infections, it certainly does not preclude the use of said antibodies to treat diseases that cannot be treated with etanercept. Furthermore, it also noted that Arora et al. indicates that anti-TNF antibodies exist which can be used to **treat diseases which cannot be treated by etanercept**, wherein said antibodies do not bind Fc receptors or fix complement (aka an antibody with greater therapeutic efficacy than etanercept, **but without side effects associated with Fc receptors or complement)**.

It is also noted that Arora et al. state that there are issues involving the in vitro assay used which raise questions about the in vivo relevance of said assay ("It should be noted, however, that the level of mTNF expression on MT-3 cells may reach supraphysiologic levels, representing a potential limitation of the functional studies.", page 130, column two).

The MPEP section 716.02(b) states:

716.02(b) [R-2] Burden on Applicant

>I. < BURDEN ON APPLICANT TO ESTABLISH RESULTS ARE UNEXPECTED AND SIGNIFICANT

*The evidence relied *>upon< should establish "that the differences in results are in fact unexpected and unobvious and of both statistical and* ***practical significance****." Ex parte Gelles, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992) (Mere conclusions in appellants' brief that the claimed polymer had an unexpectedly increased impact strength "are not entitled to the weight of conclusions accompanying the evidence, either in the specification or in a declaration."); Ex parte C, 27 USPQ2d 1492 (Bd. Pat. App. & Inter. 1992) (Applicant alleged unexpected results with regard to the claimed soybean plant, however there was no basis for judging the practical significance of data with regard to maturity date, flowering date, flower color, or height of the plant.). See also In re Nolan, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977) and In re Eli Lilly, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) as discussed in MPEP § 716.02(c).*

Regarding the various in vitro data proffered as evidence of unexpected results, it is unclear as to what the actual practical significance of said results is. As per above, Arora et al. indicates in spite of the cited in vitro results that the antiTNF antibodies referred to in the Arora declaration have clinical efficacy in diseases that etanercept cannot be used to treat. Furthermore, it also noted that Arora et al. indicates that anti-TNF antibodies exist which can be used to **treat diseases which cannot be treated by etanercept**, wherein said antibodies do not bind Fc receptors or fix complement (aka an antibody with greater therapeutic efficacy than etanercept, **but without side effects associated with Fc receptors or complement)**. Thus, said teaching calls into question the relevance of such functions to clinical effects seen using antiTNF agents. It is also noted that none of the cited in vitro studies actually used the closest prior art construct of Smith et al. Applicants comments about said construct represent conjecture unsupported by actual evidence.

In addition, Furst et al. confirm the disclosure of Arora et al. that antiTNF antibodies have increased clinical efficacy in comparison to etancerpt (see abstract). In addition,

Furst et al. disclose that there are a variety of properties unrelated to those referred to in the cited in vitro assays which can account for the superior clinical efficacy of antiTNF antibodies in comparison to etancerpt (see page 164, second column, continued on next page). Furst et al. teach that :

"Pharmacokinetic differences are profound, with the monoclonal antibodies (infliximab and adalimumab) demonstrating lower clearances, greater volumes of distribution, and longer half-lives than the soluble receptor (etanercept). Furthermore, the intravenous form of monoclonal antibody (infliximab) has greater bioavailability and shows much higher peak concentrations. This probably results in more constant and also higher peak tissue concentrations for the monoclonal antibodies, despite the differing doses and dosing regimens among the 3 drugs. These differences, in turn, may result in different effects on TNF concentrations and different effects on effector cells. Monoclonal antibodies may also eliminate activated T-cells and monocyte/macrophages directly either by cell lysis or by inducing apoptosis."(page 164, second column, last paragraph, continued on next page).".

Regarding the risk of infection and antiTNF antibodies, Furst et al. teach that said issues can be addressed during the course of treatment (see page 165, first column, last paragraph) indicating that the issue does not preclude their clinical use. None of the references of record indicate that the risk of infection precludes use of antiTNF antibodies whilst the references do indicate that said antibodies have clinical efficacy in diseases that etanercept cannot be used to treat.

Furthermore, Strand et al. teach that*:*

"TNFalpha inhibitors provide an excellent example of biologic agents with demonstrable clinical benefit despite limited knowledge regarding their in vivo mechanisms of action. Even using sophisticated in vitro and ex vivo techniques, it has been difficult to confirm whether presumed mechanisms of action occur in vivo. Possibilities include neutralization of soluble and/or transmembrane TNFalpha; crosslinking of transmembrane TNFalpha, leading to reverse signal transduction and caspase-induced apoptosis; lysis of membrane TNFalpha-expressing cells; and apoptosis of monocyte/macrophages and/or T cells via mAb-mediated signals or cytokine deprivation, illustrated in FIG. 3[90'91.] Recent data also demonstrate direct and indirect effects of TNFalpha on regulatory T-cell function[92'93.] Etanercept neutralizes lymphotoxin

in addition to TNFalpha but clinical consequences in humans have not been identified. TABLES 2,3 summarize in vitro and clinical differences between currently available antagonists." (page 83, second column).".

Thus, Arora et al, Strand et al. and Furst et al. indicate that regarding the differences between antiTNF antibodies and the claimed invention that there is no clear correlation between the in vitro properties of said agents and their in vivo function.

Regarding applicants comments about Capon et al., Capon et al. teach DNA encoding Ig/ligand binding fusion proteins (see column 5). Capon et al. teach that the Ig/ligand binding fusion protein can contain the soluble portion of a cell surface receptor (eg. the receptor minus the transmembrane and cytoplasmic domains, see column 8, first complete paragraph). Capon et al. teach that the DNA encoding the Ig portion of the fusion protein can contain at least the hinge, CH2 and CH3 domains of the constant region of an Ig heavy chain or the Fc portion of the heavy chain (see column 10, second paragraph). In fact, Capon et al., column 10, second paragraph teach that:

> *Typically, such fusions retain at least functionally active hinge, CH2 and CH3 domains of the constant region of an immunoglobulin heavy chain. Fusions are also made to the C-terminus of the Fc portion of a constant domain, or immediately N-terminal to the CH1 of the heavy chain or the corresponding region of the light chain. This ordinarily is accomplished by constructing the appropriate DNA sequence and expressing it in recombinant cell culture.*

Thus, Capon et al. clearly teach the structure of the Ig portion of the Ig fusion protein recited in the claimed inventions. In fact, Capon et al. particularly point out and disclose this structure in column 10, second paragraph (aka said disclosure encompasses a preferred embodiment). However, it also note that the MPEP section 2123 states:

PATENTS ARE RELEVANT AS PRIOR ART FOR ALL THEY CONTAIN

"The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting In re Lemelson, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)).

Regarding applicants comments about CD4 soluble fusion proteins and IL-2 fusion proteins, said soluble fusion proteins do not even contain TNF receptor and do not constitute the “closest prior art”. CD4 and IL-2 bind molecules have no relation to TNF or the TNF receptor and wherein the ligand for said CD4 molecule is not even a soluble protein (aka **it is a cell surface bound molecule**). Regarding applicant comments about anti TNF antibodies, said molecules are structurally and functionally distinct from the claimed invention. For example, said molecules do not contain a "TNF receptor” as per recited in the claimed invention. Furthermore, the binding of said antibodies is totally mediated by a unique combination of CDR/FR regions that are found in the antibody variable region wherein said CDR/FR regions are not found in the claimed invention. As per above, the closest prior art is the nucleic acid encoding an IgG1/soluble portion of a 75kD TNF receptor wherein the fusion protein is bivalent for TNF receptor as per taught by Smith et al.

Regarding applicants comments, Smith et al. teach a nucleic acid encoding an IgG1/soluble portion of a 75kD TNF receptor wherein the fusion protein is bivalent for TNF receptor (see column 10, last paragraph). Smith et al. do not teach a nucleic acid encoding an Ig/soluble portion of a 75kD TNF receptor wherein the IG portion lacks the first domain of the constant region. Capon et al. teach DNA encoding Ig/ligand binding fusion proteins (see column 5). Capon et al. teach that the Ig/ligand binding fusion protein can contain the soluble portion of a cell surface receptor (eg. the receptor minus the transmembrane and cytoplasmic domains, see column 8, first complete paragraph). Capon et al. teach that the DNA encoding the Ig portion of the fusion protein can contain at least the hinge, CH2 and CH3 domains of the constant region of an Ig heavy chain or the Fc portion of the heavy chain (see column 10, second paragraph). In fact, Capon et al., column 10, second paragraph teach that:

> *Typically, such fusions retain at least functionally active hinge, CH2 and CH3 domains of the constant region of an immunoglobulin heavy chain. Fusions are also made to the C-terminus of the Fc portion of a constant domain, or immediately N-terminal to the CH1 of the heavy chain or the corresponding region of the light chain. This ordinarily is accomplished by constructing the appropriate DNA sequence and expressing it in recombinant cell culture.*

Thus, Smith et al. teach a nucleic acid encoding an IgG1/soluble portion of a 75kD TNF receptor wherein the fusion protein is bivalent for TNF receptor (see column 10, last paragraph) whilst Capon et al. teach that such molecules can be made wherein the CH1 domain is omitted. Also, it is noted that Smith et al. teach that the fusion protein is bivalent for TNFR (aka **it contains only two copies of the TNF R molecule, see column 10, last paragraph**) wherein said molecule is produced from a single heavy constant and light chain constant region. It is further noted that the references related to etanercept indicate that said molecule has a IgG1 constant region. Claims that do not recite an IgG1 constant region encompass other IgG constant regions wherein the results related to etanerecept are not germane to constant regions other than IgG1. Regarding the Lesslauer declaration of 12/13/04, said declaration does not compare the fusion protein to the closest prior art as per above. In addition, as per above, fusion proteins containing two copies of the TNFR as per recited in the claims were already known in the art. In addition, there is still zero evidence of record regarding IgG2 and IgG4 isotypes (aka the other art known isotypes).

10. Claims 233-237,239-243,246-253,255-261,274-286 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dembic et al. (Cytokine, 1990) in view of Smith et al. (US Patent 5,395,760) Capon et al. (US Patent 5428130).

Dembic et al. teach DNA encoding an insoluble (eg. membrane bound) 75 kD TNF receptor that is derived from HL60 cells and that encodes the various peptide fragments recited in the claims (see page 231, second column). Dembic et al. teach the extracellular portion of said molecule (see abstract). The extracellular portion of the membrane bound molecule would be a soluble portion of said molecule. Dembic et al. do not teach a nucleic acid encoding an Ig/soluble portion of a 75kD TNF receptor. Smith et al. teach DNA encoding an insoluble (eg. membrane bound) 75 kD TNF receptor that has the amino acid seqeunce of SEQ. ID. NO:27 (see Figure 2). Smith et al. teach the soluble extracellular portion of said molecule (see column 4). Smith et al. teach a nucleic acid encoding an IgG1/soluble portion of a 75kD TNF receptor wherein the fusion protein is bivalent for TNF receptor (see column 10, last paragraph). Smith et al. do not teach a nucleic acid encoding an Ig/soluble portion of a 75kD TNF receptor wherein the IG portion lacks the first domain of the constant region. This rejection

addresses the seqeunce of claim 243 as encompassing SEQ. ID No 27 or the HL-60 relate seqeunce of claim 233. Capon et al. teach DNA encoding Ig/ligand binding fusion proteins (see column 5). Capon et al. teach that the Ig/ligand binding fusion protein can contain the soluble portion of a cell surface receptor (eg. the receptor minus the transmembrane and cytoplasmic domains, see column 8, first complete paragraph). Capon et al. teach that the DNA encoding the Ig portion of the fusion protein can contain at least the hinge, CH2 and CH3 domains of the constant region of an Ig heavy chain or the Fc portion of the heavy chain (see column 10, second paragraph). Capon et al. teach vectors /host cells containing said DNA and use of said cells to produce fusion protein (see column 26-30). Capon teach the use of IgG-1 constant region in said fusion proteins (see claim 3). Capon et al. teach that the ligand binding portion of the Ig/ligand binding fusion protein can be derived from a wide variety of different known cell surface receptors (see column 7, third paragraph from bottom). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Dembic et al. teach DNA encoding an insoluble (eg. membrane bound) 75 kD TNF receptor that is derived from HL60 cells, Smith et al. teach the nucleic acid sequence encoding an insoluble (eg. membrane bound) 75kD TNF receptor and DNA encoding bivalent Ig fusion proteins containing said molecule while Capon et al. teach DNA encoding soluble Ig/ligand binding fusion proteins wherein the DNA encoding the Ig portion of the fusion protein can contain at least the hinge, CH2 and CH3 domains of the constant region of an Ig heavy chain and wherein the ligand binding protein is a soluble portion derived from a cell surface receptor. One of ordinary skill in the art would have been motivated to do the aforementioned because Capon et al. teach that the ligand binding portion of the Ig/ligand binding fusion protein can be derived from a wide variety of different known cell surface receptors (see column 7, third paragraph from bottom) and that said fusion proteins have a variety of a uses (see column 4). The IgG1 constant region fragment encoding nucleic acids of pCD4Hgamma1 appear to be the art known nucleic acids encoding the portion of the human IgG1 constant region as per disclosed in Capon et al. In addition, Smith et al. teach a nucleic acid encoding an IgG1/soluble portion of a 75kD TNF receptor wherein the fusion protein is bivalent for TNF receptor.

Applicants arguments are as per addressed above.

12. Claims 233-237,239-243,246-253,255-261,274-286 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (US Patent 5,395,760) in view of Hohmann et al. (J. Biol. Chem., 1989) and Capon et al. (US Patent 5428130).

Smith et al. teach DNA encoding an insoluble (eg. membrane bound) 75 kD TNF receptor that has the amino acid seqeunce of SEQ. ID. NO:27 (see Figure 2). Smith et al. teach the soluble extracellular portion of said molecule (see column 4). Smith et al. teach DNA encoding an Ig fusion molecule. Smith et al. teach a nucleic acid encoding an IgG1/soluble portion of a 75kD TNF receptor wherein the fusion protein is bivalent for TNF receptor (see column 10, last paragraph). Smith et al. do not teach a nucleic acid encoding an Ig/soluble portion of a 75kD TNF receptor wherein the Ig portion lacks the first domain of the constant region and wherein the DNA encodes the 75 kD TNF receptor in HL-60 cells. This rejection addresses the sequence of claim 233 as encompassing other than SEQ. ID. No. 27. Smith et al. teach that nucleic acids encoding the 75 kD TNF receptor can isolated from mammalian cells that express said receptor and method for isolating said DNA (see columns 5-6). Hohmann et al. teach that HL-60 cells express the TNF 75 kD receptor (see page 14929). Whilst the identity of the sequence encoding the TNF receptor 75 kD in the construct of claim 233 is unclear, since it was apparently derived from HL60 cells it will be considered as encoding the same HL60 sequence as found in said cells. Capon et al. teach DNA encoding Ig/ligand binding fusion proteins (see column 5). Capon et al. teach that the Ig/ligand binding fusion protein can contain the soluble portion of a cell surface receptor (eg. the receptor minus the transmembrane and cytoplasmic domains, see column 8, first complete paragraph). Capon et al. teach that the DNA encoding the Ig portion of the fusion protein can contain at least the hinge, CH2 and CH3 domains of the constant region of an Ig heavy chain or the Fc portion of the heavy chain (see column 10, second paragraph). Capon et al. teach vectors /host cells containing said DNA and use of said cells to produce fusion protein (see column 26-30). Capon teach the use of IgG-1 constant region in said fusion proteins (see claim 3). Capon et al. teach that the ligand binding portion of the Ig/ligand binding fusion protein can be derived from a wide variety of different known cell surface receptors (see column 7, third paragraph from bottom). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Smith et al. teach a

nucleic acid encoding an IgG1/soluble portion of a 75kD TNF receptor wherein the fusion protein is bivalent for TNF receptor (see column 10, last paragraph) and Smith et al. teach that nucleic acids encoding the 75 kD TNF receptor can isolated from mammalian cells that express said receptor and method for isolating said DNA whilst Hohmann et al. teach that HL-60 cells express the TNF 75 kD receptor while Capon et al. teach DNA encoding soluble Ig/ligand binding fusion proteins wherein the DNA encoding the Ig portion of the fusion protein can contain at least the hinge, CH2 and CH3 domains of the constant region of an Ig heavy chain and wherein the ligand binding protein is a soluble portion derived from a cell surface receptor. One of ordinary skill in the art would have been motivated to do the aforementioned because Capon et al. teach that the ligand binding portion of the Ig/ligand binding fusion protein can be derived from a wide variety of different known cell surface receptors (see column 7, third paragraph from bottom) and that said fusion proteins have a variety of a uses (see column 4) and Smith et al. teach that nucleic acids encoding the 75 kD TNF receptor can isolated from mammalian cells that express said receptor and method for isolating whilst Hohmann et al. teach that HL-60 cells express the TNF 75 kD receptor. The IgG1 constant region fragment encoding nucleic acids of pCD4Hgamma1 appear to be the art known nucleic acids encoding the portion of the human IgG1 constant region as per disclosed in Capon et al. In addition, Smith et al. teach a nucleic acid encoding an IgG1/soluble portion of a 75kD TNF receptor wherein the fusion protein is bivalent for TNF receptor.

Applicants arguments are as per addressed above.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron, Ph.D. whose telephone number is (571)272-0851. The examiner can normally be reached on Monday-Thursday 7:30-6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ron Schwadron/
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Primary Examiner
Art Unit 1644